Paracetamol overdosing in a tertiary care hospital: implementation and outcome analysis of a preventive alert programme

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Abstract: WHAT IS KNOWN AND OBJECTIVES Paracetamol is a frequently used antipyretic and analgesic drug, but also a dose-dependent hepatotoxin. Unintentional paracetamol overdosing is a common medication error in hospitals. The present study aimed at (i) analysis of unintentional paracetamol overdosing in hospitalized patients; (ii) development, implementation and outcome analysis of an alert algorithm for the prevention of relevant paracetamol overdosing. METHODS All patients who received paracetamol in a Swiss tertiary care hospital during 2011 to 2014 were analysed to detect cases of paracetamol overdosing in a local pharmacoepidemiological database. In 2014, an automated algorithm screened the hospital's electronic prescribing system for patients at risk of overdosing, followed by expert validation. When imminent relevant overdosing was confirmed, alerts were issued to prescribers. Relevance was defined as prescriptions that permitted repeated daily paracetamol exposure of 5 g. RESULTS AND DISCUSSION From 2011 to 2013, relevant overdosing occurred in 11 patients (5-8 g/day for 3 to 5 days), which corresponds to $0 \cdot 4$ % of all patients exposed to any paracetamol overdosing (mean n = 988 per year). In 2014, alerts were issued by experts in 23 cases with subsequent changes to prescriptions in 21 ($91 \cdot 3$ %) thereof. Although the occurrence of any paracetamol overdosing declined only marginally in 2014 (n = 914), no relevant overdosing occurred anymore. WHAT IS NEW AND CONCLUSION Unintentional paracetamol overdosing was frequent but only a small fraction thereof was deemed relevant. This proof of concept study analysed local hospital data and developed a preventive system combining sensitive automated detection with subsequent specific expert validation. The resulting alerts achieved high compliance and prevented relevant paracetamol overdosing.

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Paracetamol Overdosing in a Tertiary Care Hospital: Implementation and Outcome Analysis of an Alert Program

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A Proof-of-concept for the Prevention of Medication Errors

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SUMMARY

What is known and objectives: Paracetamol is a frequently used antipyretic and analgesic drug, but also a dose-dependent hepatotoxin. Unintentional paracetamol overdosing is a common medication error in hospitals. The present study aimed at 1) Analysis of unintentional paracetamol overdosing in hospitalized patients; 2) Development, implementation and outcome of an alert algorithm for the prevention of considerable paracetamol overdosing.

Methods: All patients who received paracetamol in a Swiss tertiary care hospital during 2011 to 2014 were analysed to detect cases of paracetamol overdosing in a local pharmacoepidemiological database. In 2014 an algorithm screened the hospital's electronic prescribing system for patients at risk of considerable overdosing, followed by expert validation. When such overdosing was confirmed as imminent, alerts were issued to prescribers. Considerable overdosing was defined as prescriptions that permitted repeated daily paracetamol exposure of ≥ 5 g.

Results and Discussion: From 2011 to 2013 considerable overdosing occurred in 11 patients (5 - 8 g / d for 3 to 5 days), which corresponds to 0.4 % of all patients exposed to any paracetamol overdosing (mean n = 988 per year). In 2014 alerts were issued by experts in 23 cases with subsequent changes to prescriptions in 21 (91.3 %) thereof. While the occurrence of any paracetamol overdosing declined only marginally in 2014 (n = 914), no considerable overdosing occurred anymore.

What is new and Conclusion: This proof of concept demonstrates that analyzing local hospital data allows the development of alert algorithms that successfully prevent relevant medication errors. Unintentional paracetamol overdosing was frequent but thereof only a small fraction was deemed considerable. The presented intervention achieved a high compliance and prevented this medication error.

INTRODUCTION

Paracetamol has analgesic and antipyretic properties and is one of the most frequently used drugs worldwide. If administered within labelled doses of no more than 4 g per day severe adverse effects are very rare, but if recommended doses are exceeded it is also an intrinsic hepatotoxin.(1) Toxicity is enhanced in patients with cachexia or alcoholism and with repeated overdosing.(2, 3) Because of its over-the-counter availability and frequent use intentional and unintentional paracetamol overdosing is common in clinical practice, and paracetamol-induced liver failure is indeed the leading cause of liver transplantations in the US.(1, 4) Zhou and colleagues recently investigated the frequency of unintentional paracetamol overdosing in a tertiary care hospital and reported that 6.6% of paracetamol users exceeded the recommended maximum dose of 4 g per day.(5) Civan et al. performed a similar analysis and reported overdosing in 2.6%.(6)

In hospitals that use clinical information systems (CIS) with computerized physician order entry (CPOE) all prescriptions are electronically documented, and integrated clinical decision support systems (CDSS) may in theory detect and prevent many medication errors including paracetamol overdosing.(7, 8) However, in clinical practice automated alerts from CDSS are mostly oversensitive and clinically irrelevant.(9, 10) Such over-alerting without clinical implications may lead to alert fatigue and ultimately to indiscriminate alert overriding or deactivation of the CDSS.(11) For an effective prevention of paracetamol overdosing, alerts should therefore only be issued in clinically relevant situations, i.e. when they imply a considerable risk of adverse events and require the prescriber to take action.(12) Therefore the present study aimed to quantify considerable paracetamol overdosing and to develop, implement and evaluate the outcome of a specific preventive alert algorithm.

METHODS

We analysed paracetamol overdosing occurring in a Swiss tertiary care hospital with about 1,000 beds and 40 clinical specialty divisions. For all retrospective analyses of paracetamol overdosing we used our previously described pharmacoepidemiological database containing information on demographics, laboratory results and electronic drug prescriptions extracted on single patient-level from the hospital's CIS.(13) Of note, the hospitals CIS (KISIM by Cystec AG) features not only prescriptions, but also a confirmation for each drug's actual administration including its time.(14) The cantonal ethics committee, the hospital's medical director and the hospital's centre for clinical research had approved the extraction of anonymized patient data, setup of a pharmacoepidemiological database and analysis, and the access to patients' original medical records for research purposes. We developed and validated an algorithm for the identification of patients with confirmed paracetamol administrations of > 4 g per day and compared the time periods from 1 Jan 2011 until 31 Dec 2013 (before implementation of an alert system) vs. 1 Jan to 31 Dec 2014 (after implementation of an alert system). By reviewing comprehensive electronic medical records of patients with ≥ 2 subsequent days of overdosing the following additional information was compiled: number, dose, route of administration and Anatomical Therapeutic Chemical Classification System code (ATC-code) of prescribed and administered paracetamol containing products, cachexia, alcoholism, laboratory results of alanine amino transaminase (ALT) before and after exposure to overdose and other signs and symptoms of paracetamol-induced liver injury.

For the prevention of paracetamol overdosing we developed an algorithm within the hospitals CIS that identified patients at risk of considerable paracetamol overdosing. The algorithm was implemented in 2014 and allowed local safety experts at the Department of Clinical Pharmacology an on-demand identification of any patient with confirmed administrations of > 4 g paracetamol per calendar-day. For this, a program

based on Oracle Instant Client developed by the hospitals' IT department accessed the CIS and extracted the amount of paracetamol of any administered drug within the last calendar-day, i.e. 1 May 0:00 to 1 May 23:59.(15) This raw data was then used to calculate the total amount of paracetamol patients had received using STATA software.(16) Patients identified as receiving > 4 g were then validated through review of their electronic medical records and additional information as described above was compiled including information on prescriptions of paracetamol that were not (yet) administered, e.g. drugs prescribed 'as needed'.

Based on the results from retrospective analyses and currently available literature we classified administrations of ≥ 5 g per day for ≥ 3 subsequent days as a threshold for considerable overdosing, i.e. clinicians should take action *before* patients are exposed to such an overdose. For patients suffering from cachexia or alcoholism a lower threshold was chosen, their prescribers were alerted immediately after any administration of > 4 g / day. If our review confirmed a potential for considerable overdosing we notified prescribing physicians through internal email and if appropriate also through personal phone calls. These internal emails featured the cause of overdosing, e.g. a parallel administration of paracetamol p.o. and i.v. and a short quote of the products SPC regarding dosing in patients suffering from cachexia or alcoholism. Subsequent changes to paracetamol prescriptions were recorded.

RESULTS AND DISCUSSION

For the time period of 2011 to 2013, i.e. before implementation of the alert system, we identified 49,357 individual patients with at least one paracetamol administration during hospitalization. Among all paracetamol users 2,965 patients (6.01 %) were exposed to at least one day with administration of > 4 g paracetamol per day. Repeated overdosing with ≥ 5 g for ≥ 2 consecutive days occurred in 38 patients, and among these 4 suffered from cachexia and 2 of current alcoholism. Considerable

overdosing with administrations of 5 to 8 g paracetamol per day for up to 5 consecutive days had occurred in 11 patients. Alanine aminotransferase (ALT) values before and after exposure to considerable overdosing were available for 9 of those patients. In one patient ALT after overdosing exceeded three times the upper limit of normal. In this case, clinicians suspected paracetamol as a cause and stopped its administration after exposing this cachectic patient to 5 g paracetamol for three consecutive days.

In 2014 our proactive alert system was implemented and 19,589 individual patients received at least one paracetamol administration during hospitalization. Thereof 914 (4.67%) were exposed to at least one day with administration of > 4 g per day. The our alert system identified on average 3 patients per day that were exposed to more than 4 g of paracetamol per day. These were subject to timely review of their electronic medical records at the early morning of the following day. The assessment whether considerable overdosing was imminent took usually less than 5 minutes per patient. Alerts with recommendations to change current paracetamol prescriptions were issued for 23 patients during one year. In 21 of these cases (91.3%) prescribing physicians were compliant with our recommendations and changed paracetamol prescriptions accordingly on the same day as the alert was issued. An additional 8 alerts were issued for patients with presence of cachexia or alcoholism for which a maximum dose of 3 g per day was recommended. In 6 of those cases prescription were adapted accordingly. Following the implementation of proactive alerts considerable paracetamol overdosing of ≥ 5 g per day for more than two days did not occur anymore in 2014. Study design and results are presented in **Figure 1**.

Paracetamol overdosing is a ubiquitous and frequent medication error. In fact the proportion of patients that were exposed to more than 4 g paracetamol during their hospitalization was 6.0% in our setting and therefore almost identical to the number reported by Zhou et al. in a similar setting in the US.(5) However, a single day with administration of only little more than 4 g paracetamol, although a formal medication

error, is usually irrelevant. In order to avoid alert fatigue proactive safety systems therefore have to find an alerting threshold for medication errors that are relevant and require prescription changes. Indeed, our further analyses confirmed that the majority of paracetamol overdosing is not repeated and during three years we did not identify a single case of paracetamol-induced liver injury. Typically, overdosing occurs only once per patient and was caused by early administration of a dose actually scheduled for the next day or overlapping administrations when the route of administration was changed from oral- to i.v. or vice versa. Another at risk scenario occurs when multiple paracetamol-containing drugs are prescribed concomitantly, or when there are fixed-dose plus on-demand prescriptions of paracetamol. On the other hand unintentional iatrogenic paracetamol hepatotoxicity and even liver failure has been described and justifies preventive measures.(1) Because of the rarity of such events preventive measures must be efficient but also highly specific in order to assure physicians' compliance with alerts.

We therefore chose a pragmatic solution, i.e. an automated sensitive screening was followed by specific manual evaluations. Our experience with this system shows that once installed the necessary resources for review of prescribed overdose are minimal and that considerable paracetamol overdosing did not occur any more after the implementation of our safety system in 2014.

WHAT IS NEW AND CONCLUSION

We cannot formally prove that our program was the exclusive cause for the absence of considerable paracetamol overdosing. Yet our alert program may have had an additional effect on the prescribing behaviour regarding paracetamol. Our alert program was is part of a proactive and open drug safety culture and can serve as a proof-of-concept not only regarding considerable paracetamol overdosing but also for the prevention of other suitable medication errors. Such semi-automated safety

programs can be implemented in clinical routine of any hospital with a CIS, IT specialists and clinical drug safety experts.

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David Niedrig contributed to the study design, algorithm development and programming, data compilation and interpretation, and wrote the first version of the manuscript. Guido Bucklar and Michael Fetzer provided extracted data from CIS to establish the local pharmacoepidemiological database and implemented the automatic detection of paracetamol administrations in 2014. Sarah Mächler and Carmen Gött contributed to data compilation and interpretation. Stefan Russmann revised the manuscript and contributed to the study design, algorithm development and data interpretation.

REFERENCES

1. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42(6):1364-72.

2. Swiss Agency for Therapeutic Products, Product Information - http://www.swissmedic.ch [Internet]. 2015. Available from: http://www.swissmedicinfo.ch.

3. Larson AM. Acetaminophen hepatotoxicity. Clin Liver Dis. 2007;11(3):525-48, vi.

4. Major JM, Zhou EH, Wong HL, Trinidad JP, Pham TM, Mehta H, et al. Trends in rates of acetaminophen-related adverse events in the United States. Pharmacoepidemiol Drug Saf. 2015.

5. Zhou L, Maviglia SM, Mahoney LM, Chang F, Orav EJ, Plasek J, et al. Supratherapeutic dosing of acetaminophen among hospitalized patients. Arch Intern Med. 2012;172(22):1721-8.

6. Civan JM, Navarro V, Herrine SK, Riggio JM, Adams P, Rossi S. Patterns of acetaminophen use exceeding 4 grams daily in a hospitalized population at a tertiary care center. Gastroenterol Hepatol (N Y). 2014;10(1):27-34.

7. Radley DC, Wasserman MR, Olsho LE, Shoemaker SJ, Spranca MD, Bradshaw B. Reduction in medication errors in hospitals due to adoption of computerized provider order entry systems. J Am Med Inform Assoc. 2013;20(3):470-6.

8. Schiff GD, Amato MG, Eguale T, Boehne JJ, Wright A, Koppel R, et al. Computerised physician order entry-related medication errors: analysis of reported errors and vulnerability testing of current systems. BMJ Qual Saf. 2015;24(4):264-71.

9. Weingart SN, Simchowitz B, Padolsky H, Isaac T, Seger AC, Massagli M, et al. An empirical model to estimate the potential impact of medication safety alerts on patient safety, health care utilization, and cost in ambulatory care. Arch Intern Med. 2009;169(16):1465-73.

10. Fritz D, Ceschi A, Curkovic I, Huber M, Egbring M, Kullak-Ublick GA, et al. Comparative evaluation of three clinical decision support systems: prospective screening for medication errors in 100 medical inpatients. European journal of clinical pharmacology. 2012;68(8):1209-19.

11. Knight AM, Falade O, Maygers J, Sevransky JE. Factors associated with medication warning acceptance for hospitalized adults. J Hosp Med. 2015;10(1):19-25.

12. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to improve the usability of drug-drug interaction clinical decision support alerts. J Am Med Inform Assoc. 2015;22(6):1243-50.

13. Niedrig DF, Gött C, Fischer A, Muller ST, Greil W, Bucklar G, et al. Second-generation antipsychotics in a tertiary care hospital: prescribing patterns, metabolic profiles, and drug interactions. Int Clin Psychopharmacol. 2015;31(1):42-50.

14. Cistec AG. Clinical Information Systems 2015 [cited 2015 20 December 2015]. Available from: http://www.cistec.com.

15. Oracle Corporation. Oracle Instant Client 2015 [cited 2014 20 December 2014]. Available from: http://www.oracle.com/technetwork/database/features/instant-client/index.html.

16. StataCorp. STATA Version 13.1 2015 [cited 2014 26 May 2016]. Available from: http://www.stata.com.